

A¹
36. (Amended) The method for producing a non-pyrogenic, endotoxin-free, stroma free, cross-linked tetrameric hemoglobin of claim 35, wherein in step (B), said oxygen is removed by centrifuging the red blood cells under a vacuum sufficient to remove oxygen from the preparation.

A²
43. (Amended) The method for producing a non-pyrogenic, endotoxin-free, stroma-free, cross-linked tetrameric hemoglobin of claim 42, wherein in step (C), said oxygen is removed by centrifuging the red blood cells under a vacuum sufficient to remove oxygen from the preparation.

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-64 are pending in the application, with 7, 13, 19, 27, 35, 42, and 49 being the independent claims. Claims 36 and 43 have now been amended to correct editorial errors and clear up any matters of form.

Based on the above amendment and the following Remarks, the Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and they be withdrawn.

Rejections Under 35 U.S.C. § 112

The Examiner has rejected claims 20-26, 28-34, 36-41, and 43-64 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. The Applicant respectfully requests that the Examiner reconsider these rejections and that they be withdrawn.

The Examiner has rejected claims 20, 28, 36, 43, 52, and 59, which recite oxygen removal by centrifugation under a vacuum. The Examiner writes, "it is unclear if the centrifuging of the blood cells or the vacuum of the blood cells yields the removal of oxygen. Thus, one can not determine if a certain speed is necessary to remove the oxygen if the centrifuge is responsible for removal of oxygen. Furthermore, it is unclear what is defined as "sufficient" for the removal of oxygen." (Paper No. 8 at p. 2).

The Applicant believes, however, that the rejected claims are clearly sufficiently definite. See *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565 (Fed. Cir. 1986) ("A decision on whether a claim is invalid under § 112, 2d ¶, requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification."). The specification states at page 14 that "oxygen removal is accomplished by agitating, or even more preferably, by centrifuging, the cells while under vacuum." The specification further states at page 15 that "solutions of SFH can be readily deoxygenated by applying a vacuum sufficient to equal the partial pressure of water at the temperature of the solution, while the solution is centrifuged at a speed sufficient to produce a force greater than the surface tension of the solution. These are generally low speeds and can easily be met with preparatory centrifuges, or those of a continuous flow variety." The specification also states on

page 13 that the "extent of deoxygenation can be measured by gas chromatograph, zirconium-based detector ..., by measuring pO_2 or by measuring the spectral shift that is characteristic of deoxyhemoglobin formation." Finally, at page 13, the specification indicates the desire in the art to remove "substantially all of the oxygen present." While the disclosures referred to above are not limitations to be read into the claims, they are clearly evidence that the specification is sufficient such that "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *See Orthokinetics*. Therefore, the Applicant respectfully requests that the Examiner reconsider his rejection, and that it be withdrawn.

The Examiner has rejected claims 36 and 43 under 35 U.S.C. § 112, ¶ 2 as allegedly being indefinite for having two periods. The Applicant has deleted the second period in both claims, rendering this rejection moot. The Applicant therefore requests that the Examiner withdraw this rejection.

The Examiner writes that for claims "drawn to a method of increasing the oxygen carrying capacity of an individual, it is unclear to what the oxygen carrying capacity is being measured against." The Applicant respectfully disagrees with the Examiner and submits that "those skilled in the art would understand what is claimed." *See Orthokinetics*. In particular, it is clear from the preamble "A method of increasing the oxygen carrying capacity of an individual" that the increase is relative to before administering the claimed hemoglobin. The claims at issue here are directed to increasing the oxygen carrying capacity of a single individual. Nowhere do these claims refer to another individual. The Applicant respectfully requests that the Examiner withdraw this rejection.

The Examiner has rejected claims 23, 31, 39, 46, 55, and 62 for alleged lack of antecedent basis for the phrase "the solution" in the base claims. The Applicant respectfully directs the Examiner's attention to the claims themselves for antecedent basis for the phrase "the solution". For example, claim 23 reads in part, "wherein said process step (B) comprises centrifuging *a solution* of said cells..." (emphasis added). All of the rejected claims appear to have the proper antecedent basis. The Applicant respectfully requests that the Examiner withdraw this rejection.

Rejections Under 35 U.S.C. § 102

The Examiner has rejected claims 1-18, 27, 29, 32-34, 42, 44, and 47-64 under 35 U.S.C. § 102(b) over Tye, U.S. Patent No. 4,529,719 ("the '719 patent"). In order to sustain a rejection under 35 U.S.C. § 102, the Examiner must show that the reference over which the claims are rejected discloses all of the elements of the claimed invention. All of the rejected claims recite the two elements that the hemoglobin be non-pyrogenic and endotoxin-free, but the Examiner has not shown that the '719 patent discloses a non-pyrogenic, endotoxin-free hemoglobin. As described in the specification at p. 10, "a preparation of hemoglobin is said to be 'non-pyrogenic' if it may be administered into an individual of the same species as that from which the hemoglobin was derived ... without causing an immunologic or pyrogenic reaction." In contrast, the '719 patent merely discloses "hemoglobin free of greater than 98% of the non-heme protein" ('719 patent col. 8, ll. 35-36). However, as stated in the instant application at page 10, "a preparation of hemoglobin is said to be 'stroma-free' if the hemoglobin has been treated to remove substantially all stromal material, such that the preparation no longer exhibits the immunoreactivity to blood type antigens...". The '719 patent neither discloses nor suggests that

the hemoglobin discussed therein is sufficiently free of stromal material to avoid causing immunoreactivity.

The hemoglobin of the present invention is substantially different from that disclosed in or suggested by the '719 patent. The Examiner must consider the material limitations that the hemoglobin of the present invention is non-pyrogenic and endotoxin-free. The Applicant respectfully points out that the Examiner has admitted that the '719 patent "does not teach removing endotoxin from preparation containing red blood cells..." (Paper No. 8 at p. 4). Nor does the '719 patent teach a non-pyrogenic hemoglobin. A reference that does not teach *all* of the elements of a claim cannot anticipate that claim. In view of the lack of disclosure of such elements in the '719 patent, the Applicant respectfully requests that the Examiner reconsider his rejection, and that it be withdrawn.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 1-64 under 35 U.S.C. § 103 over the '719 patent in view of Bucci *et al.*, U.S. Patent No. 5,290,919 ("the '919 patent"). However, the '719 patent and the '919 patent, either alone or in combination, neither disclose nor suggest non-pyrogenic, endotoxin-free hemoglobin, as required by all of the claims. As described in the specification at p. 10, "a preparation of hemoglobin is said to be 'non-pyrogenic' if it may be administered into an individual of the same species as that from which the hemoglobin was derived ... without causing an immunologic or pyrogenic reaction." Without a disclosure or suggestion that the hemoglobin molecules disclosed in the '719 and '919 patents have the property of being non-pyrogenic, the Examiner's rejection cannot be maintained.

Furthermore, as described in the specification at page 11, "a preparation of hemoglobin is said to be 'endotoxin-free' if the hemoglobin has been treated to remove substantially all endotoxin. Thus, for the purposes of the present invention, endotoxin-free hemoglobin has an amount of endotoxin ranging from 0-10%, and more preferably from 0-1%, of the amount of endotoxin present in USP water. In a preferred method for forming such endotoxin-free ... hemoglobin, the hemoglobin is deoxygenated to render it 'oxygen-free.' As used herein, a preparation of hemoglobin is said to be 'oxygen-free' if the hemoglobin has been treated to remove substantially all the oxygen." The present invention provides methods for deoxygenation that are novel and non-obvious, and that produce superior results to the methods of the prior art. Thus, the present invention provides an endotoxin-free hemoglobin that is superior for being more endotoxin-free than hemoglobin of the prior art.

In view of the fact that the '719 and '919 patents, either alone or in combination, neither disclose nor suggest the non-pyrogenic endotoxin-free hemoglobin of the present invention, the Examiner's rejection should be withdrawn.

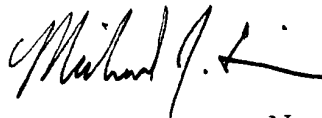
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. The Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. The Applicant believes that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If

the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Michael J. Bell", with a stylized flourish at the end.

Michael J. Bell (Reg. No. 39,604)
Michael J. Stimson (Reg. No. 45,429)

Date: June 27, 2001

HOWREY SIMON ARNOLD & WHITE, LLP
Box No. 34
1299 Pennsylvania Avenue, N.W.
Washington, D.C. 20004-2402
(202) 783-0800